

WE CLAIM:

1. A composition of matter comprising isoapoptolidin in isolated, purified form.
2. A functionalized isoapoptolidin compound comprising a modified isoapoptolidin core or a stereoisomer thereof, in which:
 - (a) at least one hydroxyl group in the isoapoptolidin core is replaced with a substituent selected from C₁-C₂₄ hydrocarbyloxy, C₂-C₂₅ acyloxy, C₂-C₂₅ haloacyloxy C₂-C₂₅ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₂₅ carbonato, halogenated C₂-C₂₅ carbonato, C₂-C₂₅ thiocarbonato, halogenated C₂-C₂₅ thiocarbonato, carbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, thiocarbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, sulfamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, and protected hydroxyl groups;
 - (b) at least one 1,3-diene functionality in the isoapoptolidin core is replaced by the product of a Diels-Alder reaction with a dienophile;
 - (c) at least one carbon-carbon double bond in the isoapoptolidin core is replaced with a carbon-carbon single bond; and/or
 - (d) at least one 1,2-diol functionality in the isoapoptolidin core is replaced with a cyclic ether.
3. The functionalized isoapoptolidin compound of claim 2, in which at least one hydroxyl group in the isoapoptolidin core is replaced with a substituent selected from C₁-C₂₄ hydrocarbyloxy, C₂-C₂₅ acyloxy, C₂-C₂₅ haloacyloxy C₂-C₂₅ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₂₅ carbonato, halogenated C₂-C₂₅ carbonato, C₂-C₂₅ thiocarbonato, halogenated C₂-C₂₅ thiocarbonato, carbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, thiocarbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, sulfamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, and protected hydroxyl groups.
4. The functionalized isoapoptolidin compound of claim 3, wherein the substituent is selected from C₁-C₁₂ hydrocarbyloxy, C₂-C₁₃ acyloxy, C₂-C₁₃ haloacyloxy C₂-C₁₃ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₁₃ carbonato, halogenated C₂-C₁₃ carbonato, C₂-C₁₃ thiocarbonato, halogenated C₂-C₁₃ thiocarbonato, carbamoyloxy, N-(C₁-C₁₂ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₁₂

5. The functionalized isoapoptolidin compound of claim 4, wherein the substituent is selected from C₁-C₁₂ hydrocarbyloxy, C₂-C₁₃ acyloxy, and tri(C₁-C₁₂ hydrocarbyl)-substituted silyloxy.

(II)

Chemical structure (II) is a complex polyketide derivative. It features a long carbon chain with multiple double bonds (conjugated and non-conjugated) and various functional groups. Key features include: a terminal sugar moiety (left) with substituents Q^5O , R^1O , and QO^1 ; a series of stereocenters with substituents OR^2 , OR^3 , and OR^4 ; and several oxygen-containing functional groups labeled QO^2 , QO^4 , QO^6 , QO^8 , QO^7 , and QO^3 . The chain is numbered from 1 to 28, with additional numbering for the sugar rings (1' to 6' and 1'' to 6''). The structure is highly branched and complex, typical of a natural product derivative.

Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are independently selected from H, C₁-C₁₂ hydrocarbyl, acyl of the formula -(CO)-R⁵ in which R⁵ is C₁-C₁₂ hydrocarbyl, and hydroxyl-protecting groups; and R¹, R², R³, and R⁴ are C₁-C₁₂ alkyl or H, or a stereoisomer thereof.

8. The compound of claim 6, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are independently selected from H, C_1-C_6 hydrocarbyl, $-(CO)-R^5$ wherein R^5 is C_1-C_6 hydrocarbyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are C_1-C_6 hydrocarbyl; and

R^1, R^2, R^3 , and R^4 are C_1-C_4 alkyl.

9. The compound of claim 8, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are independently selected from H, C_1-C_6 alkyl, $-(CO)-R^5$ wherein R^5 is C_1-C_6 alkyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are all methyl or all ethyl; and R^1, R^2, R^3 , and R^4 are methyl.

10. The compound of claim 7, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are independently selected from H, C_1-C_6 hydrocarbyl, $-(CO)-R^5$ wherein R^5 is C_1-C_6 hydrocarbyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are C_1-C_6 hydrocarbyl; and

R^1, R^2, R^3 , and R^4 are C_1-C_4 alkyl.

11. The compound of claim 10, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are independently selected from H, C_1-C_6 alkyl, $-(CO)-R^5$ wherein R^5 is C_1-C_6 alkyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are all methyl or all ethyl; and R^1, R^2, R^3 , and R^4 are methyl.

12. The compound of claim 6, wherein:

Q^1 is $-(CO)-R^5$ and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^2 and Q^3 are $-(CO)-R^5$ and Q^1, Q^4, Q^5, Q^6, Q^7 , and Q^8 are H;
 Q^3 is $-(CO)-R^5$ and $Q^1, Q^2, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^4 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^5 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^6, Q^7$, and Q^8 are H;
 Q^6 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H;
 Q^6 is C_1-C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H; or
 Q^8 is C_1-C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^6$, and Q^7 are H.

13. The compound of claim 12, wherein:

Q^1 is benzoyl and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;

Q² and Q³ are acetyl and Q¹, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q³ is acetyl and Q¹, Q², Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁴ is acetyl and Q¹, Q², Q³, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁵ is acetyl and Q¹, Q², Q³, Q⁴, Q⁶, Q⁷, and Q⁸ are H;
Q⁶ is acetyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H;
Q⁶ is methyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H; or
Q⁸ is methyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, and Q⁷ are H.

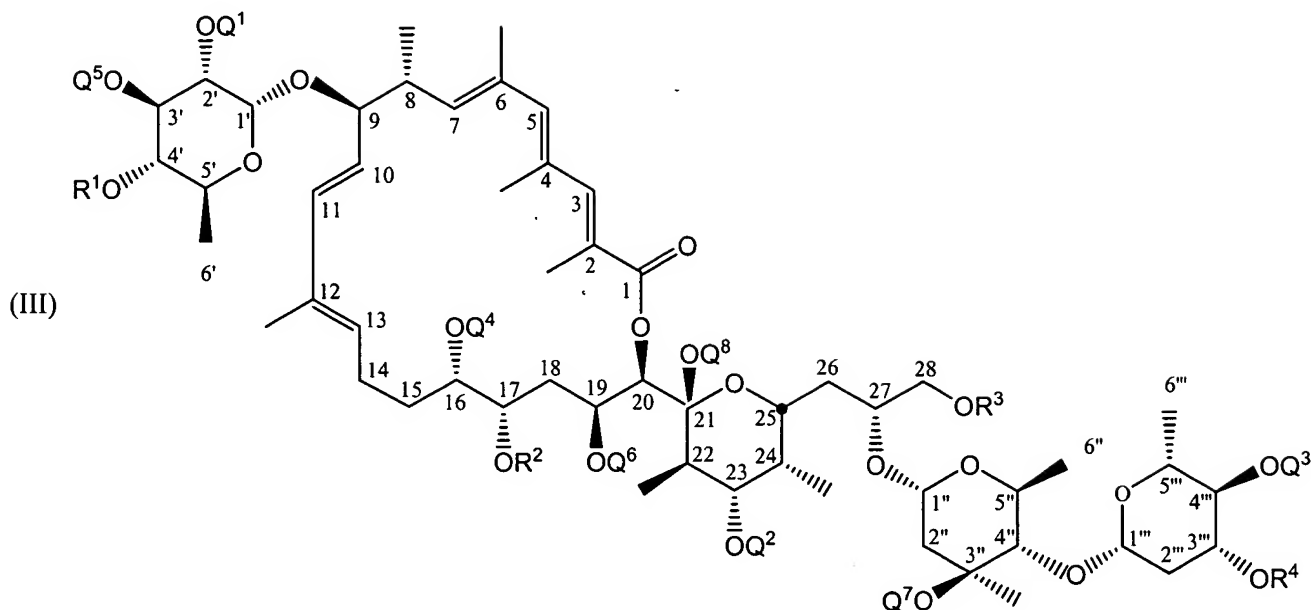
14. The compound of claim 7, wherein:

Q¹ is -(CO)-R⁵ and Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q² and Q³ are -(CO)-R⁵ and Q¹, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q³ is -(CO)-R⁵ and Q¹, Q², Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁴ is -(CO)-R⁵ and Q¹, Q², Q³, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁵ is -(CO)-R⁵ and Q¹, Q², Q³, Q⁴, Q⁶, Q⁷, and Q⁸ are H;
Q⁶ is -(CO)-R⁵ and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H;
Q⁶ is C₁-C₆ alkyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H; or
Q⁸ is C₁-C₆ alkyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, and Q⁷ are H.

15. The compound of claim 14, wherein:

Q¹ is benzoyl and Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q² and Q³ are acetyl and Q¹, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q³ is acetyl and Q¹, Q², Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁴ is acetyl and Q¹, Q², Q³, Q⁵, Q⁶, Q⁷, and Q⁸ are H;
Q⁵ is acetyl and Q¹, Q², Q³, Q⁴, Q⁶, Q⁷, and Q⁸ are H;
Q⁶ is acetyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H;
Q⁶ is methyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁷, and Q⁸ are H; or
Q⁸ is methyl and Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, and Q⁷ are H.

16. A compound having the structure of formula (III)



wherein:

Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are selected from H, C₁-C₁₂ hydrocarbyl, acyl of the formula -(CO)-R⁵ in which R⁵ is C₁-C₁₂ hydrocarbyl, and hydroxyl-protecting groups; and

R¹, R², R³, and R⁴ are C₁-C₁₂ alkyl or H, with the proviso that at least one of Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ is other than H when R¹, R², R³, and R⁴ are methyl and the compound has the stereoisomeric configuration of formula (III),

or a stereoisomer thereof.

17. The compound of claim 16, having the stereoisomeric configuration of formula (III).

18. The compound of claim 16, wherein:

Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are selected from H, C₁-C₆ hydrocarbyl, -(CO)-R⁵ wherein R⁵ is C₁-C₆ hydrocarbyl, and -Si(R⁶R⁷R⁸) wherein R⁶, R⁷, and R⁸ are C₁-C₆ hydrocarbyl; and

R¹, R², R³, and R⁴ are C₁-C₄ alkyl.

19. The compound of claim 18, wherein:

Q¹, Q², Q³, Q⁴, Q⁵, Q⁶, Q⁷, and Q⁸ are selected from H, C₁-C₆ alkyl, -(CO)-R⁵ wherein R⁵ is C₁-C₆ alkyl, and -Si(R⁶R⁷R⁸) wherein R⁶, R⁷, and R⁸ are all methyl or all ethyl; and

R¹, R², R³, and R⁴ are methyl.

20. The compound of claim 17, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are selected from H, C_1 - C_6 hydrocarbyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 hydrocarbyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are C_1 - C_6 hydrocarbyl; and R^1, R^2, R^3 , and R^4 are C_1 - C_4 alkyl.

21. The compound of claim 20, wherein:

$Q^1, Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are selected from H, C_1 - C_6 alkyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 alkyl, and $-Si(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are all methyl or all ethyl; and R^1, R^2, R^3 , and R^4 are methyl.

22. The compound of claim 16, wherein:

Q^1 is $-(CO)-R^5$ and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^2 and Q^3 are $-(CO)-R^5$ and Q^1, Q^4, Q^5, Q^6, Q^7 , and Q^8 are H;
 Q^3 is $-(CO)-R^5$ and $Q^1, Q^2, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^4 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^5 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^6, Q^7$, and Q^8 are H;
 Q^6 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H;
 Q^6 is C_1 - C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H; or
 Q^8 is C_1 - C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^6$, and Q^7 are H.

23. The compound of claim 22, wherein:

Q^1 is benzoyl and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^2 and Q^3 are acetyl and Q^1, Q^4, Q^5, Q^6, Q^7 , and Q^8 are H;
 Q^3 is acetyl and $Q^1, Q^2, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^4 is acetyl and $Q^1, Q^2, Q^3, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^5 is acetyl and $Q^1, Q^2, Q^3, Q^4, Q^6, Q^7$, and Q^8 are H;
 Q^6 is acetyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H;
 Q^6 is methyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H; or
 Q^8 is methyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^6$, and Q^7 are H.

24. The compound of claim 17, wherein:

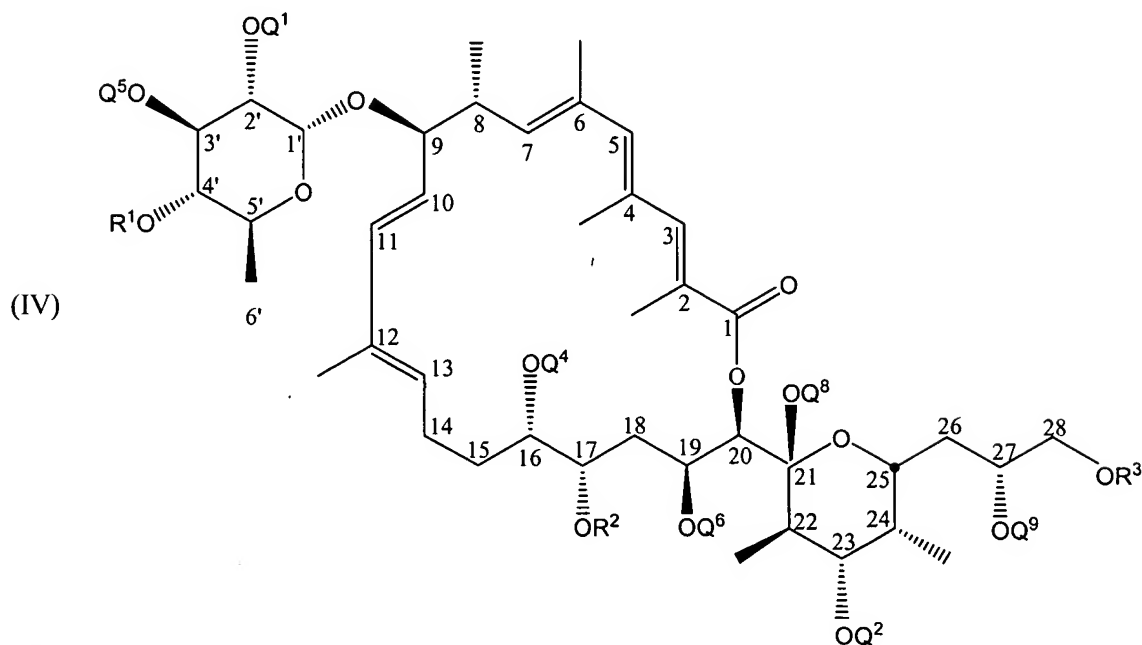
Q^1 is $-(CO)-R^5$ and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;

Q^2 and Q^3 are $-(CO)-R^5$ and Q^1, Q^4, Q^5, Q^6, Q^7 , and Q^8 are H;
 Q^3 is $-(CO)-R^5$ and $Q^1, Q^2, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^4 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^5 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^6, Q^7$, and Q^8 are H;
 Q^6 is $-(CO)-R^5$ and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H;
 Q^6 is C_1-C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H; or
 Q^8 is C_1-C_6 alkyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^6$, and Q^7 are H.

25. The compound of claim 24, wherein:

Q^1 is benzoyl and $Q^2, Q^3, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^2 and Q^3 are acetyl and Q^1, Q^4, Q^5, Q^6, Q^7 , and Q^8 are H;
 Q^3 is acetyl and $Q^1, Q^2, Q^4, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^4 is acetyl and $Q^1, Q^2, Q^3, Q^5, Q^6, Q^7$, and Q^8 are H;
 Q^5 is acetyl and $Q^1, Q^2, Q^3, Q^4, Q^6, Q^7$, and Q^8 are H;
 Q^6 is acetyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H;
 Q^6 is methyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^7$, and Q^8 are H; or
 Q^8 is methyl and $Q^1, Q^2, Q^3, Q^4, Q^5, Q^6$, and Q^7 are H.

26. A compound having the structure of formula (IV)



wherein:

$Q^1, Q^2, Q^4, Q^5, Q^6, Q^8$, and Q^9 are independently selected from H, C_1 - C_{12} hydrocarbyl, acyl of the formula $-(CO)-R^5$ in which R^5 is C_1 - C_{12} hydrocarbyl, and hydroxyl-protecting groups; and R^1, R^2 , and R^3 are independently selected from C_1 - C_{12} alkyl and H, or a stereoisomer thereof.

27. The compound of claim 26, having the stereoisomeric configuration of formula (IV).

28. The compound of claim 26, wherein:

$Q^1, Q^2, Q^4, Q^5, Q^6, Q^8$, and Q^9 are independently selected from H, C_1 - C_6 hydrocarbyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 hydrocarbyl, and $-\text{Si}(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are C_1 - C_6 hydrocarbyl; and R^1, R^2 , and R^3 are C_1 - C_4 alkyl.

29. The compound of claim 28, wherein:

$Q^1, Q^2, Q^4, Q^5, Q^6, Q^8$, and Q^9 are independently selected from H, C_1 - C_6 alkyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 alkyl, and $-\text{Si}(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are all methyl or all ethyl; and R^1, R^2 , and R^3 are methyl.

30. The compound of claim 27, wherein:

$Q^1, Q^2, Q^4, Q^5, Q^6, Q^8$, and Q^9 are independently selected from H, C_1 - C_6 hydrocarbyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 hydrocarbyl, and $-\text{Si}(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are C_1 - C_6 hydrocarbyl; and R^1, R^2 , and R^3 are C_1 - C_4 alkyl.

31. The compound of claim 30, wherein:

$Q^1, Q^2, Q^4, Q^5, Q^6, Q^8$, and Q^9 are independently selected from H, C_1 - C_6 alkyl, $-(CO)-R^5$ wherein R^5 is C_1 - C_6 alkyl, and $-\text{Si}(R^6R^7R^8)$ wherein R^6, R^7 , and R^8 are all methyl or all ethyl; and R^1, R^2 , and R^3 are methyl.

32. A compound prepared by reaction of the compound of claim 6 with a dienophile under conditions effective to result in a Diels-Alder reaction at the C-10/C-13 diene functionality.

33. A compound prepared by reaction of the compound of claim 16 with a dienophile under conditions effective to result in a Diels-Alder reaction at the C-10/C-13 diene functionality.

34. A compound prepared by reaction of the compound of claim 26 with a dienophile under conditions effective to result in a Diels-Alder reaction at the C-10/C-13 diene functionality.

35. The compound of any one of claims 32, 33, and 34, wherein the dienophile is an N-halosuccinimide.

36. A compound prepared by reaction of the compound of claim 6 with a reagent and under conditions effective to hydrogenate at least one carbon-carbon double bond.

37. A compound prepared by reaction of the compound of claim 16 with a reagent and under conditions effective to hydrogenate at least one carbon-carbon double bond.

38. A compound prepared by reaction of the compound of claim 26 with a reagent and under conditions effective to hydrogenate at least one carbon-carbon double bond.

39. A compound prepared by reaction of the compound of claim 6 with a nucleophilic co-reactant and under conditions effective to result in nucleophilic addition to at least one carbon-carbon double bond.

40. A compound prepared by reaction of the compound of claim 16 with a nucleophilic co-reactant and under conditions effective to result in nucleophilic addition to at least one carbon-carbon double bond.

41. A compound prepared by reaction of the compound of claim 26 with a nucleophilic co-reactant and under conditions effective to result in nucleophilic addition to at least one carbon-carbon double bond.

42. A compound prepared by reaction of the compound of claim 6 with a reagent effective to result in conversion of at least one 1,2-diol functionality to a cyclic ether.

43. A compound prepared by reaction of the compound of claim 16 with a reagent effective to result in conversion of at least one 1,2-diol functionality to a cyclic ether.

44. A compound prepared by reaction of the compound of claim 26 with a reagent effective to result in conversion of at least one 1,2-diol functionality to a cyclic ether.

45. A pharmaceutical composition comprising a therapeutically effective amount of the compound of claims 1, 2, 6, 16, or 26 and a pharmaceutically acceptable carrier.

46. The composition of claim 45, wherein the therapeutically effective amount is a unit dosage and the composition is composed of a unit dosage form.

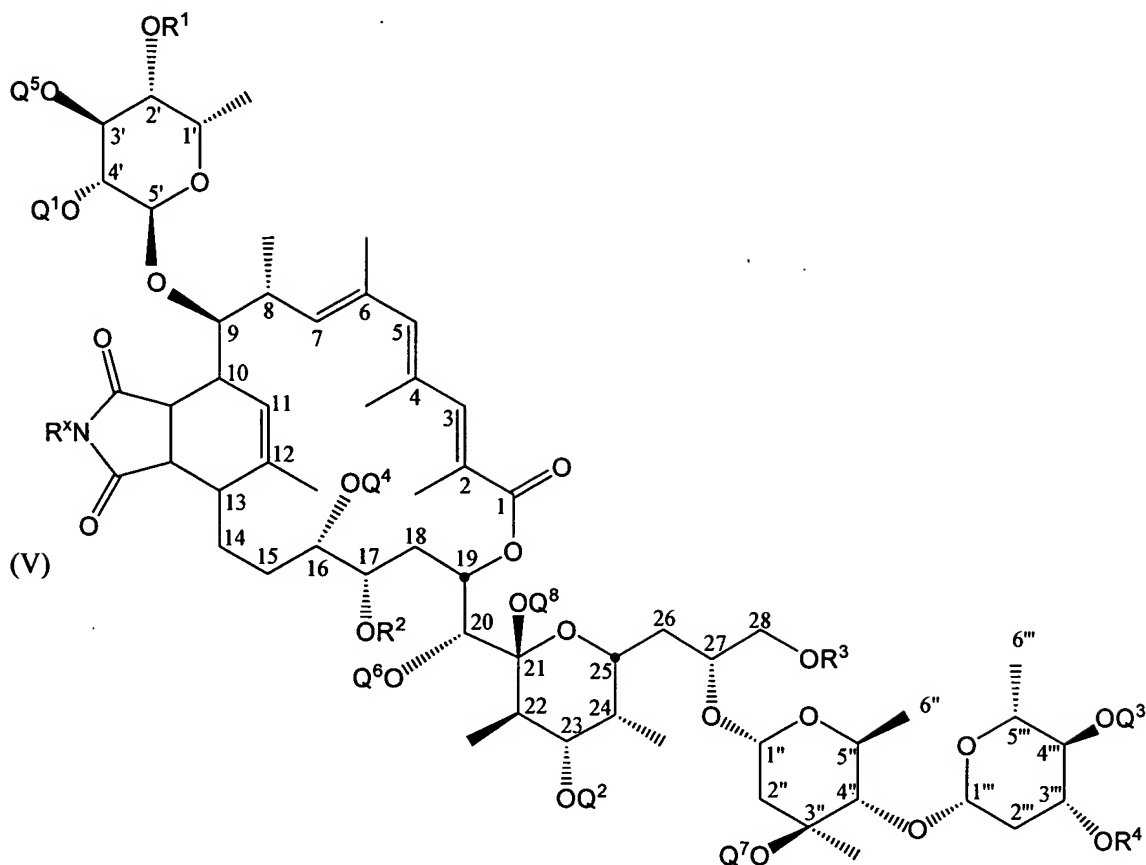
47. The composition of claim 45, comprising a sustained release formulation.

48. A method for treating a mammalian patient in need of treatment for a disorder responsive to apoptosis, comprising administering to the patient a therapeutically effective amount of a compound of claims 1, 2, 6, 16, or 26 and a pharmaceutically acceptable carrier.

49. The method of claim 48, wherein the disorder is cancer.

50. A composition of matter comprising deglycosylated isoapoptolidin in isolated, purified form.

51. A compound having the structure of formula (V)



wherein:

Q^1 , Q^2 , Q^3 , Q^4 , Q^5 , Q^6 , Q^7 , and Q^8 are independently selected from H, C_1 - C_{12} hydrocarbyl, acyl of the formula $-(CO)-R^5$ in which R^5 is C_1 - C_{12} hydrocarbyl, and hydroxyl-protecting groups; and R^1 , R^2 , R^3 , and R^4 are C_1 - C_{12} alkyl or H, or a stereoisomer thereof.

52. Compounds prepared by oxidatively cleaving the C-20/C-21 bond in the compound of claim 51.

53. Compounds prepared by oxidatively cleaving the C-22/C-23 bond in the compound of claim 51.

54. A functionalized apoptolidin compound comprising a modified apoptolidin core in which:

(a) at least one hydroxyl group in the apoptolidin core is replaced with a substituent selected from C₁-C₂₄ hydrocarbyloxy, C₂-C₂₅ acyloxy, C₂-C₂₅ haloacyloxy, C₂-C₂₅ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₂₅ carbonato, halogenated C₂-C₂₅ carbonato, C₂-C₂₅ thiocarbonato, halogenated C₂-C₂₅ thiocarbonato, carbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, thiocarbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, sulfamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, and protected hydroxyl groups;

(b) at least one 1,3-diene functionality in the apoptolidin core is replaced by the product of a Diels-Alder reaction with a dienophile;

(c) at least one carbon-carbon double bond in the apoptolidin core is replaced with a carbon-carbon single bond; and/or

(d) at least one 1,2-diol functionality in the apoptolidin core is replaced with a cyclic ether.

55. The functionalized apoptolidin compound of claim 54, in which at least one hydroxyl group in the isoapoptolidin core is replaced with a substituent selected from C₁-C₂₄ hydrocarbyloxy, C₂-C₂₅ acyloxy, C₂-C₂₅ haloacyloxy, C₂-C₂₅ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₂₅ carbonato, halogenated C₂-C₂₅ carbonato, C₂-C₂₅ thiocarbonato, halogenated C₂-C₂₅ thiocarbonato, carbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted carbamoyloxy, thiocarbamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted thiocarbamoyloxy, sulfamoyloxy, N-(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, N,N-di(C₁-C₂₄ hydrocarbyl)-substituted sulfamoyloxy, and protected hydroxyl groups.

56. The functionalized apoptolidin compound of claim 55, wherein the substituent is selected from C₁-C₁₂ hydrocarbyloxy, C₂-C₁₃ acyloxy, C₂-C₁₃ haloacyloxy, C₂-C₁₃ thioacyloxy, C₂-C₂₅ thiohaloacyloxy, C₂-C₁₃ carbonato, halogenated C₂-C₁₃ carbonato, C₂-C₁₃ thiocarbonato, halogenated C₂-C₁₃ thiocarbonato, carbamoyloxy, N-(C₁-C₁₂ hydrocarbyl)-substituted carbamoyloxy, N,N-di(C₁-C₁₂ hydrocarbyl)-substituted carbamoyloxy, thiocarbamoyloxy, N-(C₁-C₁₂ hydrocarbyl)-substituted thiocarbamoyloxy, N,N-di(C₁-C₁₂ hydrocarbyl)-substituted thiocarbamoyloxy, sulfamoyloxy, N-(C₁-C₁₂ hydrocarbyl)-substituted sulfamoyloxy, N,N-di(C₁-C₁₂ hydrocarbyl)-substituted sulfamoyloxy, (C₁-C₆ alkoxy)methyl ether, (C₁-C₆ alkylthio)methyl ether, and tri(C₁-C₁₂ hydrocarbyl)-substituted silyloxy.

57. The functionalized apoptolidin compound of claim 56, wherein the substituent is selected from C₁-C₁₂ hydrocarbyloxy, C₂-C₁₃ acyloxy, and tri(C₁-C₁₂ hydrocarbyl)-substituted silyloxy.